REMARKS

Claims 1, 37, 40-41, 43, 54-55 and 58-62 are amended and claim 39, 46-53 and 63-69 are canceled.

I. Response to Claim Rejection under 35 U.S.C. § 102 based on Migaly (WO 2004/010932)

Claims 1, 37, 41, 43-45, 54-55 and 59-62 are rejected under 35 U.S.C. § 102(b), as allegedly being anticipated by Migaly (WO 2004/010932, Filing date 25th July 2003 which claims priority to provisional U.S. application dated 30th July 2002) referenced in the [instant] IDS filed February 15, 2006).

Applicants traverse the rejection as improper.

WO '932 does not qualify as prior art with respect to the present application.

The Examiner applies WO '932 as a reference under 35 U.S.C. § 102(b). However, WO '932 was not published more than one year prior to the effective US filing date of the present application of December 25, 2003, based on the filing date of International Application, Ser. No. PCT/JP2003/016724. Thus, WO '932 does not qualify as a reference under 35 U.S.C. § 102(b).

The Examiner further mentions that WO '932 claims priority to a US Provisional Application filed July 2003[1]. However, the prior filed US provisional applications can not be relied on as prior art under 35 U.S.C. § 102(b) since they were not published. Further, WO '932 can not be applied as a reference under 35 U.S.C. § 102(e) based on the US Provisional

[1] The serial number of the Provisional Application filed on July 25, 2003 is not provided on the face of the WO '932 publication.

Applications to which it claims priority or its International filing date of July 25, 2003, because the international application does not designate the US.

In order for a WO publication to qualify as a reference under 35 U.S.C. §102(e), the international application must meet the following three conditions:

(1) an international filing date on or after November 29, 2000;

(2) designated the United States; and

(3) published under PCT Article 21(2) in English.

In this case, the WO '932 international application does not designate the United States and therefore, the WO '932 publication can not be applied as a reference as of its international filing date, its date of completion of the 35 U.S.C. §371(c)(1), (2) and (4) requirements, or any earlier filing date to which such an international application claims benefit or priority. The WO '932 publication may only be applied as a reference under 35 U.S.C. §102(a) or (b) as of its publication date, or 35 U.S.C. §102(e) as of any later U.S. filing date of an application that properly claimed the benefit of the international application (if applicable). MPEP §2136.03 (II). In this case the WO '932 publication was published on February 5, 2004, which is after the effective US filing date of the present application as set forth above.

Accordingly, Applicants respectfully request withdrawal of the rejection.

II. Response to Claim Rejections - 35 U.S.C. § 103

A. Wong in view of Winans and further in view of Harvey et al

Claims 1, 37-39, 41, 43-49, 51-57 and 59-69 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Wong et al (U.S. 2002/156067, already of record) in view of Winans (American Journal of Health-System and Pharmacy, vol. 60, Dec. 1, 2003; page 2437-2447, already of record) further in view of Harvey et al for the reasons of record.

Although not mentioned in the rejection, the Examiner also refers to Owens as teaching that citalopram and escitalopram are also serotonin reuptake inhibitors.

Applicants traverse the rejection for the reasons of record, which are incorporated by reference herein and additionally based on the following.

The Examiner admits that Wong et al does not specifically teach metabolites of aripiprazole or dehydroaripiprazole, etc., or wherein aripiprazole is anhydrous aripiprazole crystals B or the norepinephrine reuptake inhibitor to be specifically escitalopram or citalopram. To remedy the deficiencies of Wong, the Examiner relies on Winans and Harvey et al.

Winans qualifies as a reference under 35 U.S.C. § 102(a) based on its publication date of December 1, 2003. Applicants further note that Winans article was originally published as a drug monograph in April 2003 by the University HealthSystem Consortium (see the grey box with the UHC logo). Both of these publication dates are prior to Applicants' effective US filing date of December 25, 2003, based on the International Application, Ser. No. PCT/JP2003/016274.

Applicants claim foreign priority to JP 2002-379003 which was filed in Japan on December 27, 2002, prior to both of the publication dates of the Winans article. Thus, by

submitting the English translation of Japanese priority Appln. No. 2002-379003, enclosed herewith, which provides §112 support for the present claims, Applicants remove Winans as prior art under 35 U.S.C. §102(a).[2]

In this connection Applicants note that the priority application does not specifically mention escitalopram, but as recognized by the Examiner and those of ordinary skill in the art, escitalopram is one of the enantiomers of citalopram (S-enatiomer). Furthermore, at the time of the priority date of the present application, it was known to those skilled in the art that citalopram has a similar function as that of escitalopram. In this regard, for example, Applicants refer to the underlined descriptions of Abstract in "Primary Care Companion J Clin Psychiatry as attached as Attachment A. Furthermore, Applicants refer to the underlined descriptions in Fig. 3 and CONCLUSIONS on page 23 which indicate that the activity of a racemic body citalopram is attributable to the S-enantiomer, escitalopram. The other enantiomer, i.e., the R enantiomer, is almost inactive. It is therefore evident that the pharmacological activity of citalopram and escitalopram is similar in function; escitalopram is at least twice as active as citalopram.

Thus, the disclosure of the priority application supports the present claims and Winans is removed as a reference.

Harvey et al (and/or Owens) does not remedy the deficiencies of Wong. Thus, even if the references were combined the claimed invention would not have been achieved. For at least this reason, the present invention is patentable over the cited references.

[2] Verification of the English translation will be submitted to complete the record.

Further, the present invention provides unexpectedly superior results as shown by the comparative test data provided in the Declaration under 37 C.F.R. §1.132 previously submitted on March 18, 2009.

In the Action dated June 24, 2009, the Examiner states that the Rule 132 Declaration submitted March 18, 2009, is not persuasive allegedly because the unexpected results are not commensurate in scope with the claimed invention. Specifically, the Examiner states that the data disclosed by the Applicants does not include a combination of aripiprazole or dehydroaripiprazole with citalopram which is instantly claimed in instant claims 39, 47, 57 and 64. The Examiner further asserted that the testing was carried out with very specific parameters such as the dosage of aripiprazole was 0.01 mg/kg and the dosages used for the SRI drugs differed, e.g., duloxetine, venlafaxine, escitalopram and paroxetine was used at 10 mg/kg, milnacipram was used at 30 mg/kg and sertraline was used at 3 mg/kg. The aripiprazole was injected IP in a specific vehicle which is 0.1 % acetic acid-saline followed by oral administration of the SRI in a specific vehicle which is 5% gum arabica-distilled water. As such the two drugs in the combination were administered sequentially by different routes of administration.

However, applicants disagree and submit that the previously submitted Declaration sufficiently shows the synergistic effects of the combination of agents in the present application, which are completely unexpected from the references.

In general, there are two experimental paradigms to investigate synergistic qualitative effects of two different drugs as follows:

As for reactivity in an intended test, investigating unexpected enhancement in the intended reaction when the drugs are concomitantly used at a dosage for weak or medium function separately; or

As for reactivity in an intended test, investigating whether the intended reaction would occur when the drugs are concomitantly used at a dosage which is non-effective for the parameter when used separately.

In the experiments conducted in relation to the present application, it was found, with respect to aripiprazole and various anti-depressants, that the two drugs can exert the intended anti-depression effect only if the pharmacological functions of each of the drugs are co-used in a test where an ineffective dosage for each drug is used, i.e. in the test paradigm (b) mentioned above. In other words, what was intended in the test was to qualitatively investigate whether the pharmacological functions of the two drugs can exert a synergistic anti-depression effect.

As the result, the test established that when the two drugs exist in the animal body they show an anti-depressant effect by the interactions thereof, so that a skilled artisan would understand that the two drugs can exert an anti-depression effect only if the pharmacological functions of each of the drugs are qualitatively co-used, i.e., the two drugs have a synergistic effect.

Regarding the Examiner's comments with respect to the dosages and the sequence of addition, Applicants submit that the specific dosages and the sequence of addition can be taken arbitrarily to more clearly establishing the synergistic effect of aripiprazole and an antidepressant.

More specifically, as for the sequence of addition, it is a matter of fact to employ a method for administering to an animal by which an antidepressant effect achieved by the pharmacological function of aripiprazole would be most evidently expressed. It would not be obligatory to follow the routes described in the application to investigate the intended pharmacological effect. Furthermore, in the test snbmitted in the Declaration, the effect was

indeed qualitatively detected. Thus, it is considered that the drugs used in the test would exert the same pharmacological effect as long as the drugs are absorbed into the body, irrespective of the route of addition.

As for 0.01 mg/kg and IP used in the present test, this dosage and route were employed because aripiprazole does not show an anti-depressant effect at the dosage of 0.01 mg/kg and the IP route is thought to be the most appropriate for drugs to exert an anti-depressant effect. The dosage was adjusted for mice considering the difference in the drug metabolism between humans and mice. Therefore, the difference in the dosages and the route of addition between humans and mice would not be expected to have an effect on the results obtained.

Furthermore, the different dosages among the anti-depressants for the concomitant use were employed as the dosages for each anti-depressant so as not to exert an effect of shortening the immobility time in the forced swimming test. Such dosages differ from one drug to another.

As such, the data collected and submitted in the Declaration previously filed on March 18, 2009 are appropriate not only scientifically but logically.

Moreover, the data provided in the specification as filed such as in Example 9, also establishes that the results for this combination are unexpectedly superior when compared to the data provided in the Declaration regarding the comparative examples of Wong. Even though the test method employed in the test of Example 9 is different from that for the forced swimming test, an antidepressant effect can be detected in either test. The meaning of the pharmacological function on the parameter obtained, i.e., the time required for the animal put into an environment which is impossible to cope with to get rid of the escape activity, is the same in the forced swimming test and tail suspension test. As such either test was aimed for investigating the same pharmacological function, so that a skilled artisan would easily understand that the data

presented as Example 9 is also for investigating the significant anti-depressant effect of aripiprazole and citalopram at the non-effective dosages for each drug in separate use.

As for Wong et al, as is clearly understood from the submitted Declaration and Example 9 disclosed in the original English specification, the present concomitant use (aripiprazole and citalopram or escitalopram) clearly shortens the prolonged immobility time in the forced swimming test of mice and tail suspension test (indicating that they have anti-depression effects). On the other hand, the concomitant use described in Wong et al, (risperidone, olanzapine or clozapine and reboxetine) did not significantly shorten the prolonged immobility time in the forced swimming test of mice (indicating that they tend to deteriorate).

On the other hand, as is clearly understood from the submitted Declaration and Example 9 disclosed in the original English specification, the present concomitant use (aripiprazole and citalopram or escitalopram) have a synergistic effect. In other words, the concomitant use of aripiprazole and citalopram or escitalopram reduces the administration dosage for each drug, leading to lower side-effects and is excellent in safety.

In summary, Wong et al does not disclose nor suggest the inventive combination or the advantageous effects of the present invention at all. The Winans reference does not remedy the deficiencies of Wong et al for the reasons of record, which are incorporated herein, and Winans is removed as prior art. Therefore, the present invention is patentable over the cited art for these additional reasons.

Accordingly, Applicants respectfully request withdrawal of the §103 obviousness rejection.

B. WO '932 in view of Winans

Claims 1, 37-39, 41, 43-49, 51-57 and 59-69 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Migaly (WO 2004/010932, referenced in the IDS) in view of Winans (American Journal of Health-System and Pharmacy, Vol. 60, Dec. 1, 2003; page 2437-2447, already of record).

Applicants traverse the rejection.

WO '932 is not prior art to the present application for the reasons set forth above and Winans does not disclose, teach or suggest all elements of the claimed invention. Moreover, Winans is removed as a reference as set forth above.

Accordingly, Applicants respectfully request withdrawal of the rejection.

C. Wong and Winans or WO '932 and Winans and further in view of Bando et al

Claim 40 and 58 is rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Wong and Winans or WO '932 and Winans as applied to claims 1, 37-39, 41, 43-49, 51-57 and 59-69 above, and further in view of Bando et al (U.S. 2004/0058935, PCT filing date of Sept. 25, 2002).

Applicants traverse the rejection.

WO '932 is not prior art to the present application for the reasons set forth above and Winans does not disclose, teach or suggest all elements of the claimed invention. Moreover, Winans is removed as a reference as set forth above.

Bando et al does not remedy the deficiencies of the remaining reference Wong. Thus, even if the references were combined the claimed invention would not have been achieved.

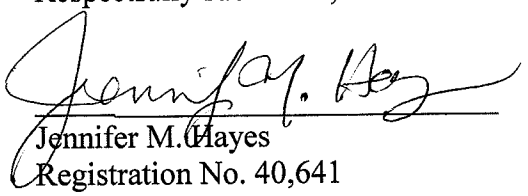
Accordingly, Applicants respectfully request withdrawal of the rejection.

II. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



Jennifer M. Hayes
Registration No. 40,641

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: October 26, 2009

Stereoisomers in Psychiatry: The Case of Escitalopram

William J. Burke, M.D., and Christopher J. Kratochvil, M.D.

Many medications in common clinical use consist of "mirror image" isomers that differ only in the direction in which they rotate plane-polarized light. These stereoisomers exist as mixtures of "right" and "left" handed molecules that are the product of chemical syntheses. However, the biochemical milieu of the human body is a highly stereospecific environment where the fit of medication and receptor may depend on the shape of the molecule in 3-dimensional space. Recent advances in chemistry have allowed the more ready preparation of single isomers of various drugs that were previously available only as racemic mixtures. For those compounds in which the isomers differ in stereospecificity, this separation into single isomers can result in significant changes in potency, tolerability, and efficacy. This article reviews some basic information about stereochemistry and describes the development of a new single isomer antidepressant, escitalopram, which is one of the components of the widely used selective serotonin uptake inhibitor citalopram.

(Primary Care Companion J Clin Psychiatry 2002;4:20–24)

Received Jan. 9, 2002; accepted March 11, 2002. From the Department of Psychiatry, University of Nebraska, Omaha.

Grant/research support provided by Forest Laboratories.

Dr. Burke has received honoraria from and is a speakers/advisory board member for Forest Laboratories.

Corresponding author and reprints: William J. Burke, M.D., Department of Psychiatry, University of Nebraska Medical Center, Omaha, NE 68198-5580 (wjburke@unmc.edu).

Among Louis Pasteur's many accomplishments was his discovery that some organic molecules exist as mirror images. Pasteur made this discovery in 1848 while experimenting with tartaric acid, a by-product of wine-making. He was able to resolve 2 crystal forms of this compound and then manually separate them on the basis of their visibly different structures. The separation was conducted with the aid of a microscope and a small set of forceps. He proceeded to make solutions of the 2 crystal forms and found they were identical in physicochemical properties with the exception of their ability to rotate plane-polarized light (Figure 1).[1]

In 1874, Jacobus H. van't Hoff provided the explanation for why these crystals rotated light differently. He hypothesized that the carbon atom had a tetrahedral structure. When 1 atom of carbon binds to 4 different substituents in a tetrahedral structure, 2 configurations are possible that are mirror images of each other. Such compounds are said to be "chiral," and the carbon is considered a chiral center (Figure 2).[1]

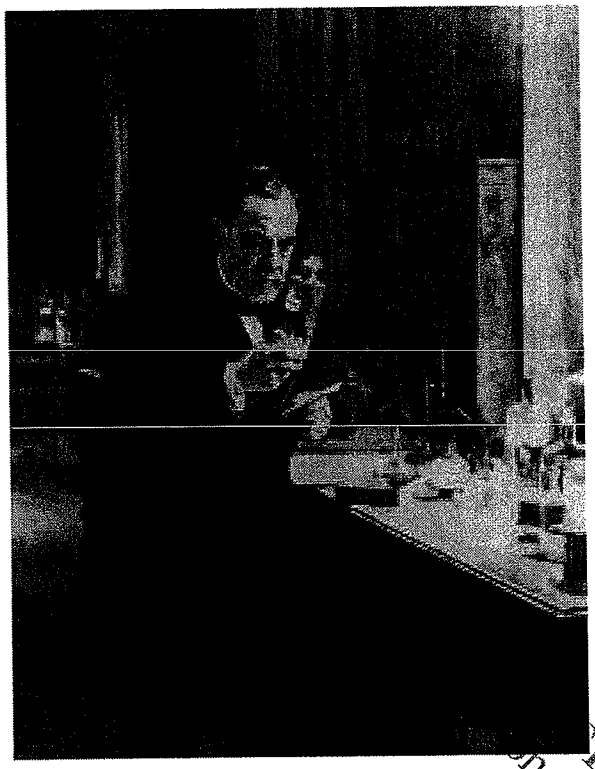
The word chiral is derived from the Greek word *cheir*, which means hand. Just like a hand or glove, chiral molecules are non-superimposable mirror images. Because of the orientation of the 4 groups around the carbon, these "stereoisomers" interact with the surrounding environment in unique ways. This stereospecificity can result in important stereoselectivity of the individual molecules at receptors. *Enantiomers* is the term for stereoisomers that are non-superimposable mirror images of one another. The presence of 1 chiral center in a molecule gives rise to a pair of enantiomers. If there is more than 1 chiral center, the yield is 2^n stereoisomers, where "n" is the number of chiral centers, and half as many pairs of enantiomers. Isomers that are not enantiomers are called "diastereomers."[3] Since enantiomers differ in their ability to rotate plane-polarized light, they are also referred to as optical isomers.[3]

TERMINOLOGY

The proper designation of enantiomers can be confusing since there are at least 3 different systems to classify them. The first is the "*d/l*" or "(+)/(–)" system that relies on the direction that the compound rotates plane-polarized light. Enantiomers that rotate plane-polarized light to the right are termed dextrorotatory (indicated by a [+] or "*d*" before the name of the compound), and those that rotate light to the left are termed levorotatory (indicated by a [–] or "*l*" prefix).[3] A racemic mixture is indicated by either a "(+)/(–)" or a "*d/l*" prefix. Interestingly, rotation of light is not an absolute property of a compound but can vary in different settings. For example, the active stereoisomer of chloramphenicol is dextrorotatory in alcohol and levorotatory in ethyl acetate.[3] Likewise, ibuprofen and naproxen are dextrorotatory as their free acids but levorotatory as their sodium salts.[3] Most drugs with a chiral center produced by chemical synthesis are available only as racemates since chemical synthesis usually leads to a racemic mixture.[4]

The other 2 classification schemes for designating enantiomers can be used once the structure has been deter-

Figure 1. Louis Pasteur, Discoverer of Stereoisomers[a]



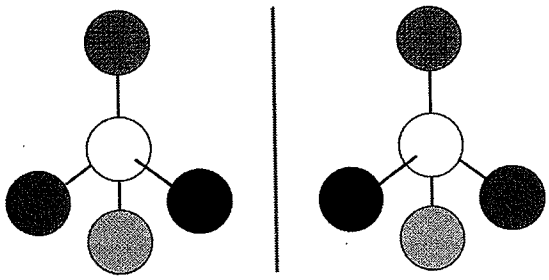
[a]Reprinted with permission from Pennisi.[2] In 1848, Louis Pasteur discovered that organic compounds may be composed of isomers that are non-superimposable, mirror-images of each other, having identical physical properties, except that they rotate a plane of polarized light in opposite directions.

mined. The older "D/L" system (no relationship to the "*d/l*" system noted above) assigns a label based on comparison to a standard reference compound, either the carbohydrate D-glyceraldehyde or the amino acid L-serine. This designation, however, now is used only for carbohydrates and amino acids.

The current system assigns a prefix of either an "*R*" (rectus) or an "*S*" (sinister) on the basis of assigning priority to the atoms attached to the chiral center. The atoms attached to the chiral center are ranked by atomic number, with the highest atomic number given the highest priority. The molecule is then viewed from the side opposite the group with the lowest priority, and a prefix is assigned according to convention. The absolute configuration nomenclature "*R/S*" has no relationship to the rotational prefixes "*d*" and "*l*" obtained by measurement of the rotation of light.

It is not unusual for stereoisomers to differ significantly in their activity for a particular function or to have a high degree of stereoselectivity for one action, but no stereoselectivity for another action.[4] The term *eutomer* is used to denote the more active enantiomer, and *distomer*, the less active. The "eudismic ratio" is the potency ratio between the eutomer and distomer.

Figure 2. Basic Structure of Stereoisomers[a]



[a]Stereoisomers have the same chemical structure but different spatial arrangement of substituent groups around the chiral center, usually a carbon atom. Enantiomers are a subtype of stereoisomers that are non-superimposable, mirror images of each other.

An important concept for medications is that although enantiomers differ only in how they rotate plane-polarized light, they may have very different biological properties in the human body. For example, the *R*-enantiomer of the chemical carvone has the odor of spearmint, while *S*-carvone smells like caraway. Enantiomers with stereospecific indications are dextropropoxyphene and levopropoxyphene. Dextropropoxyphene (Darvon) is marketed as an analgesic, while levopropoxyphene (once marketed as Novrad—*Darvon* spelled backward) is an antitussive.[5] Similarly, the toxicity of a compound may be selective for an enantiomer. The *S*-enantiomer of ketamine produces an anesthetic effect, while the *R*-enantiomer can cause hallucinations. These diverse effects reflect the fact that most biological systems consist of chiral environments, thus the orientation of a molecule in space may be crucial. A right-handed molecule may fit perfectly in a chiral protein receptor, while the enantiomer may exhibit much less activity because of its inability to fit in that receptor. This is expressed as "Pfeiffer's rule," which states that the more potent a drug is, the more likely it is to show stereoselectivity of action as a consequence of the greater steric demand for tight receptor binding.[6]

POTENTIAL ADVANTAGES OF ENANTIOMERS

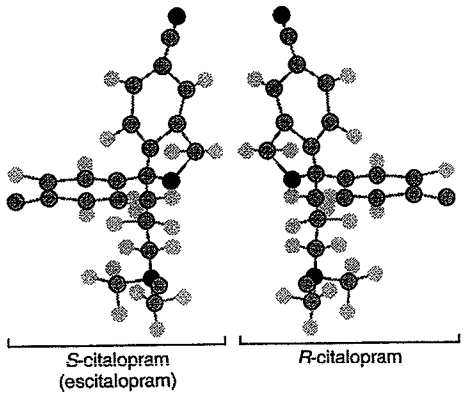
It has been argued that giving drugs as racemates is a form of polypharmacy driven by chemical rather than therapeutic considerations. Racemic mixtures can also be considered compounds that contain a 50% impurity.[3] Using a single enantiomer can result in an improved therapeutic index resulting from presumed higher potency and selectivity while removing those side effects that may be due to the less active enantiomer. Use of a single enantiomer thus can result in an improved onset of action and duration of action and a decrease in the propensity for drug-drug interactions.[7] Importantly, single stereoisomers have less complex pharmacokinetic profiles and less complex plasma concentration–effect relationships.[3] When a

Table 1. Pharmacologic Properties of the Enantiomers of Fluoxetine and Citalopram[a]

Drug	Monoamine Uptake Inhibition, IC_{50} (nM)		
	Serotonin	Norepinephrine	Dopamine
Citalopram			
Racemic citalopram	1.8	6,100	40,000
S-citalopram	1.5	2,500	65,000
R-citalopram	250	6,900	54,000
Racemic desmethylcitalopram	14	740	28,000
S-desmethylcitalopram	10	1,500	34,000
R-desmethylcitalopram	65	500	25,000
Fluoxetine			
Racemic fluoxetine	20	1,230	2,880
S-fluoxetine	22	2,040	2,510
R-fluoxetine	35	562	2,820
Racemic norfluoxetine	45	2,400	2,190
S-norfluoxetine	14	4,270	2,750
R-norfluoxetine	209	3,720	2,140

[a]Adapted with permission from Zane and Baker.[8]

Figure 3. Structure of *R*- and *S*-Citalopram[a]



[a]The selective serotonin reuptake inhibitor antidepressant citalopram is a racemic compound, composed of 2 isomers in equal proportion: the *S*-isomer and the *R*-isomer. The effect of citalopram to inhibit serotonin reuptake has been shown to reside almost exclusively in the *S*-isomer, also known as escitalopram. (Structural diagram provided by Forest Laboratories.)

racemate is given, the patient is really being given 2 different drugs with different pharmacokinetic and pharmacodynamic profiles. Other advantages of stereochemically pure drugs are reducing the total dose given and removing a source of intersubject variability.[6]

Caldwell has made the point that the "pharmacokinetic importance of drug stereochemistry depends on the mechanism of the process under consideration: passive processes such as diffusion across membranes do not involve macromolecular interactions and stereochemistry has little influence, but when the drug interacts with an enzyme or a transporter system then discrimination may be seen."[6(p40)] These are precisely the types of interactions seen in the use of psychotropic medications in which the drug needs to interact with a receptor to have its effect. This effect may entirely depend on the spatial configuration of the molecule that confronts the receptor.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Of the currently available selective serotonin reuptake inhibitors (SSRIs), fluvoxamine lacks a chiral center, whereas paroxetine and sertraline have always been available as single enantiomers.[8] Sertraline, which has 2 chiral centers (and thus 4 different enantiomers), is marketed as the *1S*(+)-,*4S*(+)-enantiomer.[8] Citalopram and fluoxetine are marketed as racemates, although the potential for reintroducing each of these drugs as one of their respective stereoisomers has been investigated.[7,8] Fluoxetine and its main metabolite, norfluoxetine, are present as enantiomers. The *R*(–)- and *S*(+)-enantiomers of fluoxetine are roughly equivalent inhibitors of serotonin uptake (Table 1).[8] On the other hand, *S*(+)-norfluoxetine is a more potent serotonin reuptake inhibitor than the *R*(–)-enantiomer. When patients are treated with racemic fluoxetine, the ratio of *S*(+)-fluoxetine/*R*(–)-fluoxetine has been reported to vary from 1 to 3.5.[8] *R*(–)-fluoxetine tends to be eliminated more rapidly, but in the presence of a cytochrome P450 2D6 enzyme (CYP2D6) inhibitor the ratio decreases. Furthermore, the *R*(–)-enantiomers of fluoxetine and norfluoxetine are weaker inhibitors of CYP2D6 than the corresponding *S*(+)-enantiomers.[9] The more rapid elimination of *R*(–)-fluoxetine and its decreased potential for drug-drug interactions led to efforts to develop this compound as a specific enantiomer for the treatment of depression. This effort was abandoned due to concerns about the possibility of corrected QT interval prolongation with *R*(–)-fluoxetine when administered as a single isomer.

In the case of citalopram (Figure 3), the *S*(+)-enantiomer (whose generic name is escitalopram) is greater than 2 orders of magnitude more potent than *R*(–)-citalopram in vitro as an inhibitor of serotonin (5-HT) uptake.[10,11] The eudismic ratio for citalopram has been calculated to be 167.[11,12] Furthermore, escitalopram has very little effect on other receptors, making it the most selective SSRI.[10,13] The plasma concentration of the eutomer of citalopram (escitalopram) is usually one third of the total citalopram concentration, with the implication being that the other two thirds of the total citalopram concentration is drug that is mainly inactive as an antidepressant.[12]

In a study of 29 depressive patients treated with various doses (20–80 mg/day) of citalopram,[12] the concentrations of the distomer were higher than those of the eutomer with a mean *S/R* ratio of 0.56 and a range of 0.32 to 0.97. In those same subjects, the mean *S/R* ratio of desmethylcitalopram (the main metabolite of citalopram) was 0.72. This study noted that escitalopram and *R*(–)-citalopram levels correlated strongly ($r = 0.866$, $p < .0001$), as did those of the desmethyl metabolites ($r = 0.932$, $p < .0001$). The implication is that enantiomers of citalopram may be metabolized by the same enzymes but at different rates.[12] This difference in the rate of metabolism would presum-

ably be due to stereoselective metabolism by the cytochrome P450 enzyme system. Levels of desmethylcitalopram observed in steady-state conditions generally reach less than 50% of those of the parent compound, leading to the suggestion that the role of *S*(+)-desmethylcitalopram in the overall activities of escitalopram can probably be ignored.[9]

Unlike the situation with fluoxetine, for which both enantiomers appear to have significant effects as antidepressants, a wealth of information from animal models suggests that the psychotropic properties of citalopram reside almost exclusively in the *S*(+)-enantiomer. For example, the effect of acute intravenous administration of citalopram and its enantiomers on neuronal activity of 5-HT cells in the rat dorsal raphe nucleus (DRN) was measured using extracellular single unit recording.[14] Escitalopram and citalopram, but not *R*(–)-citalopram, reduced the firing activity of 5-HT cells in the DRN in a dose-dependent fashion. Escitalopram was twice as potent as citalopram in this model. In the forced swim test, one of the most widely used animal models for depression, both citalopram and escitalopram demonstrated a dose-dependent reduction in immobility in mice, while *R*(–)-citalopram was inactive in this model.[15] In the rat "resident-intruder" paradigm, escitalopram was 2 to 4 times more potent than racemic citalopram.[16]

The lack of antidepressant activity of *R*(–)-citalopram in these models is certainly consistent with the IC_{50} data presented in Table 1. It is also consistent with Pfeiffer's rule, noted above, which suggests that the more potent the drug, the more likely it is to be stereoselective. In the chiral environment of the 5-HT receptor, it can be pictured that the *R*-enantiomer binds much less readily to the receptor than escitalopram. The "key" simply does not fit the "lock."

Clinical studies with escitalopram for the treatment of major depression have been conducted and provide further evidence of the potency and efficacy of escitalopram. A fixed-dose, placebo-controlled, randomized clinical trial of 10 and 20 mg of escitalopram, 40 mg of citalopram, and placebo was conducted.[17] This trial showed efficacy for all active drugs compared with placebo, but additionally that the 10-mg dose of escitalopram was at least as efficacious as 40 mg of citalopram while having an overall rate of side effects comparable to placebo. Additionally, there was a trend for the 20-mg dose of escitalopram to have greater efficacy than 40 mg of citalopram.

One of the potential benefits of using a eutomer mentioned above is that a more rapid onset of action may be realized. For antidepressants, a lag time of 3 to 4 weeks is considered standard. It is therefore of interest that escitalopram, at both doses, was statistically superior to placebo early in the study, and this superiority was reflected in multiple measures of depression.[17] For example, scores on the depressed mood item of the Hamilton Rating Scale for Depression (HAM-D) significantly decreased by the end of week 1 compared with placebo. Additionally, the overall scores on the HAM-D and Montgomery-Asberg Depression Rating Scale (MADRS) separated by the end of week 2. This finding has been further explored in a report that pooled data from 3 placebo-controlled, randomized clinical trials comparing escitalopram and citalopram with placebo in depressed outpatients.[18] The pooled data, which include data from the study by Burke and colleagues[17] mentioned above, demonstrated that the mean change from baseline in MADRS scores was significantly greater at week 1 with escitalopram, while citalopram did not significantly separate from placebo until week 6. Similar changes were seen in the mean change from baseline in the Clinical Global Impressions-Improvement (CGI-I) scale. Escitalopram treatment significantly decreased CGI-I scores within 1 week, whereas citalopram treatment significantly decreased CGI-I scores at week 4.

CONCLUSIONS

The Nobel Prize for Chemistry in 2001 was awarded to the scientists who created catalysts that could produce 1 stereoisomer without creating the mirror-image compound. The ability to synthesize a single isomer has opened the way to produce drugs that are more selective and "pure." Chemical synthesis is no longer limited to producing racemic mixtures that contain unwanted stereoisomers. In the case of citalopram, this has allowed the division of the stereoisomer that contains all of the desired activity of the racemic mixture, escitalopram, from its much less potent counterpart, *R*(–)-citalopram.

Additional studies will need to be done to elucidate the ultimate place of escitalopram in the armamentarium of medications used to treat depression, but at present it appears to hold promise as a potent, effective, and well-tolerated antidepressant that may offer a more rapid onset of action than other antidepressants for some patients.

Drug names: citalopram (Celexa), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), paroxetine (Paxil), propoxyphene (Darvon and others), sertraline (Zoloft).

REFERENCES

1. Brocks DR, Jamali F. Stereochemical aspects of pharmacotherapy. Pharmacotherapy 1995;15:551–564
2. Pennisi E. Parasitology. Close encounters: good, bad, and ugly. Science 2000;290:1491–1493
3. Hutt AJ, Tan SC. Drug chirality and its clinical significance. Drugs 1996;52(suppl 5):1–12
4. Eichelbaum M. Enantiomers: implications and complications in developmental pharmacology. Dev Pharmacol Ther 1992;18:131–134
5. Wainer IW. Three-dimensional view of pharmacology. Am J Hosp Pharm 1992;49(9, suppl 1):S4–S8
6. Caldwell J. Stereochemical determinants of the nature and consequences of drug metabolism. J Chromatogr A 1995;694:39–48
7. Tucker GT. Chiral switches. Lancet 2000;355:1085–1087
8. Lane RM, Baker GB. Chirality and drugs used in psychiatry: nice to know or need to know? Cell Mol Neurobiol 1999;19:355–372

9. Baumann P, Rochat B. Comparative pharmacokinetics of selective serotonin reuptake inhibitors: a look behind the mirror. Int Clin Psychopharmacol 1995;10(suppl 1):15–21
10. Owens MJ, Knight DL, Nemeroff CB. Second-generation SSRIs: human monoamine transporter binding profile of escitalopram and R-fluoxetine. Biol Psychiatry 2001;50:345–350
11. Hyttel J, Bøges KP, Perregaard J, et al. The pharmacological effect of citalopram resides in the (S)-(+)-enantiomer. J Neural Transm Gen Sect 1992;88:157–160
12. Rochat B, Amey M, Baumann P. Analysis of enantiomers of citalopram and its demethylated metabolites in plasma of depressive patients using chiral reverse-phase liquid chromatography. Ther Drug Monit 1995;17: 273–279
13. Sanchez C, Hyttel J. Comparison of the effects of antidepressants and their metabolites on reuptake of biogenic amines and on receptor binding. Cell Mol Neurobiol 1999;19:467–489
14. Mitchell PJ, Hogg S. Beavioural effects of escitalopram predict potent antidepressant activity. Presented at the 7th World Congress of Biological Psychiatry; July 1–6, 2001; Berlin, Germany
15. Sanchez C, Hogg S. The antidepressant effect of citalopram resides in the S-enantiomer (Lu 26-054). Presented at the 55th annual meeting of the Society of Biological Psychiatry; May 11–13, 2000; Chicago, Ill
16. Mitchell P, Hogg S. Escitalopram: rapid antidepressant activity in rats. Presented at the 7th World Congress of Biological Psychiatry; July 1–6, 2001; Berlin, Germany
17. Burke WJ, Gergel I, Bose A. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. J Clin Psychiatry 2002;63:331–336
18. Gorman JM, Korotzer A, Su G. Efficacy comparison of escitalopram and citalopram in the treatment of major depressive disorder: pooled analysis of placebo-controlled trials. CNS Spectrums 2002;7(suppl 1):40–44